The added value of health-related quality of life as a prognostic indicator of overall survival and progression-free survival in glioma patients: a meta-analysis based on individual patient data from randomised controlled trials

Coomans, Marijke ; Dirven, Linda ; Aaronson, Neil K ; Baumert, Brigitta G ; van den Bent, Martin ; Bottomley, Andrew ; Brandes, Alba A ; Chinot, Olivier ; Coens, Corneel ; Gorlia, Thierry ; Herrlinger, Ulrich ; Keime-Guibert, Florence ; Malmström, Annika ; Martinelli, Francesca ; Stupp, Roger ; Talacchi, Andrea ; Weller, Michael ; Wick, Wolfgang ; Reijneveld, Jaap C ; Taphoorn, Martin J B ; EORTC Quality of Life Group and the EORTC Brain Tumor Group

Abstract: OBJECTIVE Prognostic value of health-related quality of life (HRQoL) data may be important to inform patients in clinical practice and to guide clinical decision-making. Our study investigated the added prognostic value of HRQoL for overall survival (OS) and progression-free survival (PFS) in a large heterogeneous sample of glioma patients, besides known prognostic factors. METHODS We included individual baseline data from previously published randomised controlled trials (RCTs) in glioma patients in which HRQoL was assessed through the European Organisation for Research and Treatment of Cancer QLQ-C30 and QLQ-BN20 questionnaires. Multivariable Cox regression models (stratified for newly diagnosed versus recurrent disease) were constructed, first with clinical variables (age, sex, tumour type, performance status, allocated treatment and extent of resection) only and subsequently with HRQoL variables added, separately for OS and PFS. The added prognostic value of HRQoL was calculated using C-indices. RESULTS Baseline HRQoL and clinical data from 15 RCTs were included, comprising 5217 patients. In the model including both clinical and HRQoL variables, better cognitive and role functioning and less motor dysfunction were independently associated with longer OS, whereas better role and cognitive functioning, less nausea and vomiting and more appetite loss were independently associated with prolonged PFS. However, C-indices indicated only a small prognostic improvement of the models for OS and PFS when adding HRQoL to the clinical prognostic variables (+1.1% for OS and +.7% for PFS). CONCLUSION Our findings demonstrate that several baseline HRQoL variables are independently prognostic for OS and PFS, yet the added value of HRQoL to the known clinical prognostic variables was small.

DOI: https://doi.org/10.1016/j.ejca.2019.05.012

Keime-Guibert, Florence; Malmström, Annika; Martinelli, Francesca; Stupp, Roger; Talacchi, Andrea; Weller, Michael; Wick, Wolfgang; Reijneveld, Jaap C; Taphoorn, Martin J B; EORTC Quality of Life Group and the EORTC Brain Tumor Group (2019). The added value of health-related quality of life as a prognostic indicator of overall survival and progression-free survival in glioma patients: a meta-analysis based on individual patient data from randomised controlled trials. European Journal of Cancer, 116:190-198.
DOI: https://doi.org/10.1016/j.ejca.2019.05.012

The added value of Health-Related Quality of Life (HRQoL) as a prognostic indicator of overall survival and progression-free survival in glioma patients: a meta-analysis based on individual patient data from randomized controlled trials

Marijke Coomans[1], Linda Dirven[1,2], Neil Aaronson[3], Brigitta G. Baumert[4,5], Martin van den Bent[6], Andrew Bottomley[7], Alba A. Brandes[8], Olivier Chinot[9], Corneel Coens[7], Thierry Gorlia[10], Ulrich Herrlinger[11], Florence Keime-Guibert[12], Annika Malmström[13], Francesca Martinelli[7], Roger Stupp[14], Andrea Talacchi[15], Michael Weller[16], Wolfgang Wick[17], Jaap C. Reijneveld[18] and Martin J.B. Taphoorn[1,2], on behalf of the EORTC Quality of Life Group and the EORTC Brain Tumor Group

[1] Department of Neurology, Leiden University Medical Center, Leiden, Netherlands

[2] Department of Neurology, Haaglanden Medical Center, Den Haag, Netherlands

[3] Division of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

[4] Department of Radiation-oncology, University Hospital Bonn, Germany

[5] Department of Radiation Oncology (MAASTRO clinic), and GROW (School for Oncology and Developmental Biology), Maastricht University Medical Center, Maastricht, The Netherlands

[6] the Brain Tumor Center at, Erasmus MC Cancer Institute, Rotterdam, Netherlands

[7] Quality of Life Department, European Organisation for Research and Treatment of Cancer, Brussels, Belgium

[8] Department of Medical Oncology, Azienda USL-IRCCS Institute of Neurological Sciences, Bologna, Italy

[9] Aix-Marseille Univ, APHM, CNRS, INP, Inst Neurophysiopathol, CHU Timone, Service de Neuro-Oncologie, Marseille, France

[10] European Organization for Research and Treatment of Cancer Headquarters, Brussels, Belgium

[11] Division of Clinical Neurooncology, Department of Neurology, University of Bonn Medical Center, Bonn, Germany

[12] Groupe Hôpital Pitié-Salpetrière, Paris, France

[13] Division of Cell Biology, Department of Clinical and Experimental Medicine, Faculty of Health Sciences, Linköping University, Linköping, Sweden

[14] Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

[15] Department of Neurosciences, Azienda Ospedaliera San Giovanni Addolorata, Roma, Italia

[16] Department of Neurology, University Hospital and University of Zurich, Zurich, Switzerland.

[17] Neurology Clinic and National Centre for Tumour Diseases, University Hospital Heidelberg, Heidelberg, Germany; German Consortium of Translational Cancer Research (DKTK), Clinical Cooperation Unit Neurooncology, German Cancer Research Center, Heidelberg, Germany

[18] Department of Neurology and Brain Tumour Center Amsterdam, Amsterdam University Medical Center, Amsterdam, the Netherlands

Short title: Added prognostic value of HRQoL in glioma patients

Corresponding author:

Marijke Coomans, MSc

Leiden University Medical Center, Department of Neurology

PO BOX 9600, 2300 RC Leiden, the Netherlands

Tel: +31 71 52 61899; Fax: +31 71 524 8253

Email: m.b.coomans@lumc.nl

Funding: This study was funded with a grant from The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group.

Keywords Glioma, health-related quality of life (HRQoL), prognostic factor, brain tumor, survival.

Conflict of interest: none related to the content of this manuscript

Authorship: BB, MB, AAB, OC, UH, FKG, AM, RS, MW and WW were the principal investigators of the RCTs for which the data was originally collected, and were involved in data collection. In addition, JR and MT were also involved in data collection in several RCTs. All authors were involved in the conceptualization of this study. MC and LD performed the statistical analysis and wrote the first draft of the manuscript. All authors have been involved in the revision of the manuscript and have read and approved the final version.

Total word count (including abstract, references, tables and figure legends, excluding supplementary tables, figures and references): 4536

Abstract word count: 249

Abstract

Objective: Prognostic value of health-related quality of life (HRQoL) data may be important to inform patients in clinical practice and to guide clinical decision-making. Our study investigated the added prognostic value of HRQoL for overall survival (OS) and progression-free survival (PFS) in a large heterogeneous sample of glioma patients, besides known prognostic factors.

Methods: We included individual baseline data from previously published randomized controlled trials (RCTs) in glioma patients in which HRQoL was assessed through the EORTC QLQ-C30 and QLQ-BN20 questionnaires. Multivariable Cox regression models (stratified for newly-diagnosed versus recurrent disease) were constructed, first with clinical variables (age, sex, tumor type, performance status, allocated treatment and extent of resection) only, and subsequently with HRQoL variables added, separately for OS and PFS. The added prognostic value of HRQoL was calculated using C-indices.

Results: Baseline HRQoL and clinical data from 15 RCTs were included, comprising 5217 patients. In the model including both clinical and HRQoL variables, better cognitive and role functioning and less motor dysfunction were independently associated with longer OS, whereas better role and cognitive functioning, less nausea and vomiting and more appetite loss were independently associated with prolonged PFS. However, C-indices indicated only a small prognostic improvement of the models for OS and PFS when adding HRQoL to the clinical prognostic variables (+1.1% for OS and +0.7% for PFS).

Conclusion: Our findings demonstrate that several baseline HRQoL variables are independently prognostic for OS and PFS, yet the added value of HRQoL to the known clinical prognostic variables was small.

Introduction

Health-related quality of life (HRQoL) is an important endpoint, both in clinical practice and in clinical trials in oncology. In clinical trials, HRQoL data may contribute to determine the net clinical benefit of a treatment strategy. In clinical practice, HRQoL data may provide important information on the patients' functioning during the course of disease, and guide tailored treatment.[1,2] This is particularly important in patient populations where survival is relatively short and where cure is not possible. HRQoL is therefore relevant for patients with gliomas, the most common malignant primary brain tumor in adults[3].

One important feature of HRQoL data may be its potential prognostic value for survival. Clinical variables such as age and performance status have proven to be important prognostic factors for overall survival (OS) in glioma patients, and recent studies have shown that HRQoL is an independent prognostic marker for survival in various other cancer populations[4-6]. If demonstrated to be an independent prognostic factor in glioma, HRQoL data could be used in clinical practice to inform patients, facilitate decision-making and ultimately to improve outcomes. In addition, HRQoL could be used as a stratification variable in future clinical trials[7].

The few studies that have investigated HRQoL as a prognostic factor for survival in glioma patients reported disparate results[8-10]; in glioblastoma and anaplastic oligodendroglioma patients, the specific HRQoL scales that were found to be of prognostic importance differed between studies, and the predictive ability of the models showed only modest improvement when adding HRQoL scales to known clinical predictors[8,9]. These findings may, in part, reflect methodological issues such as small sample sizes, missing baseline data, and statistical techniques chosen to analyze the data. Moreover, prognostic models in glioma research focused on OS as endpoint. In glioma, progression-free survival (PFS) may also be a relevant outcome, which can be seen as a surrogate endpoint for measuring treatment efficacy[11]. With this knowledge, it seems most appropriate to assess the prognostic value of HRQoL for both OS and PFS. Additionally, a prognostic model should include the recent changes in

classification of tumor types involving molecular markers[12,13]. The added prognostic value of HRQoL in such a model has not yet been investigated.

The aim of the present study was to investigate the added prognostic value of HRQoL for OS and PFS in a large, heterogeneous sample of glioma patients above and beyond the known prognostic factors.

Methods

Study sample

This study is part of the CODAGLIO (i.e. COmbining clinical trial DAtasets in GLIOma) project, in which a database was created including HRQoL data of individual glioma patients from 15 previously published phase II and III randomized controlled trials (RCTs) (see supplementary Table 1 for an overview). RCTs that assessed HRQoL with the European Organization for Research and Treatment of Cancer (EORTC) questionnaires were selected for inclusion. All patients gave their informed consent to participate in the RCTs, and all principal investigators of these RCTs gave permission for use of the collected data. In all RCTs, HRQoL was assessed as a secondary endpoint.

HRQoL assessment

HRQoL data in the included trials were assessed with the EORTC QLQ-C30 version 3.0[14], in conjunction with the EORTC brain cancer-specific QLQ-BN20[15]. The EORTC QLQ-C30 is the core EORTC questionnaire that includes 30 items, comprising five functioning scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status scale, and six single items (dyspnea, appetite loss, insomnia, constipation, diarrhea, and financial difficulties). The QLQ-BN20 was specifically designed for brain tumor patients and consists of 20 items, comprising four symptom scales (future uncertainty, visual disorder, motor dysfunction, and communication deficit) and seven single items (headaches, seizures, drowsiness, hair

loss, itchy skin, weakness of legs and bladder control)[16]. For both questionnaires, raw scores were linearly transformed to a scale from 0 to 100 according to the standard EORTC guidelines[17]. For the functioning scales and the global health status scale, a higher score indicates better functioning. For the symptom scales and single items, higher scores indicate more symptoms and worse functioning. In all RCTs, baseline questionnaires were administered before the start of the allocated treatment, but after surgery and irrespective of supportive treatment such as anti-epileptic drugs (AEDs) and corticosteroids.

Other prognostic variables

Sociodemographic and clinical variables previously recognized as prognostic for OS that were available in all included RCTs were collected: tumor type (WHO grade II or III astrocytoma, oligodendroglioma, and oligoastrocytoma (all classified as non-glioblastoma), or grade IV (glioblastoma)), age, sex, disease stage (newly-diagnosed versus recurrent), WHO performance status (PS) (0 versus 1 versus 2), prior resection (yes versus no), and allocated treatment (radiotherapy (RT monotherapy), chemotherapy (chemo monotherapy), angiogenesis inhibitors (angio monotherapy), tumor-treating fields (TTF monotherapy), radiotherapy and chemotherapy combined (RT and chemo), radio and angiogenesis inhibitors combined (RT and angio), radiotherapy combined with chemotherapy and angiogenesis inhibitors (RT and chemo and angio) and chemotherapy and TFF combined (chemo and TTF)). Prior resection was classified into yes/no, because information on the extent of resection (biopsy, partial or gross total resection) was not available for all patients. Therefore, we classified both partial and complete resection as resected, and biopsy as not resected. Due to the variety of treatments that were used in the different RCTs, treatments were categorized based on type and combination (e.g., lomustine, irinotecan, combined procarbazine, lomustine and vincristine (PCV) and temozolomide were all classified as chemotherapy).

Although prognostic for survival, data on use of corticosteroids at baseline (yes/no) and data on use of AEDs at baseline (yes/no) were not available for all patients. To analyze the added prognostic value of HRQoL in a model including these factors, we conducted a subgroup analysis in the group of patients with available data for these variables. Likewise, data on molecular parameters were also only available for a selection of the patients (i.e. in more recent RCTs): isocitrate dehydrogenase (IDH) mutations (30%), co-deletion of chromosomal arms 1p and 19q (35%), and O^6-methylguanine-DNA methyltransferase (MGMT) promotor methylation (64%). Therefore, another subgroup analysis was performed in patients with information on the molecular parameters IDH and 1p/19q, which allowed reclassification of tumor type following the 2016 WHO classification[12]. MGMT status was also included in this analysis (MGMT-methylated versus MGMT-unmethylated versus MGMT status unknown).

Statistical analysis

All patients with a completed baseline HRQoL form were included in the analyses. OS was measured from the date of randomization until the date of death (i.e. event), or the date of last contact (determined at the time of the database lock, separately for each individual RCT; i.e. censored patients), and was estimated using the Kaplan-Meier method. PFS was measured from the date of randomization until the date of progression or death (i.e. events), or date of last contact (determined at the time of the database lock, separately for each individual RCT; i.e. censored patients). In all included RCTs, progression was defined by means of the Response Assessment in Neuro-Oncology Criteria (RANO) or MacDonald criteria[18,19]. The log-rank test was used to compare survival distributions. To evaluate if there were differences between patients with and without a HRQoL form (i.e., selection bias), several clinical characteristics were compared using the Chi-square test for categorical data and independent Student's t-tests for continuously distributed variables.

The construction of the final prognostic models was based on two steps. First, univariable Cox proportional hazard (CPH) models were constructed to assess the association between each

independent variable (tumor type, age, sex, prior resection, WHO performance status and all HRQoL scales/items) and OS and PFS. Hazard ratios (HRs) and their corresponding 95% two-sided confidence intervals (CI) were calculated[20]. Subsequently, multivariable CPH models, separately for OS and PFS, were constructed, including those variables that exhibited P<.10 in univariable analysis. The models were stratified for disease stage (newly-diagnosed versus recurrent). First, proportional hazard assumptions for the Cox models were assessed graphically, and potential multicollinearity was investigated with Spearman-rank correlation coefficients. Next, a stepwise backward model was applied to eliminate non-significant parameters, with a criterion of P<0.05 for inclusion and a criteria of P>0.10 for exclusion. The model was first carried out with the sociodemographic/clinical variables only ('clinical model'), and subsequently with the sociodemographic/clinical variables and HRQoL scales ('clinical + HRQoL model'). The purpose of this second model was to assess the potential benefit of adding baseline HRQoL scores to the sociodemographic/clinical factors to predict survival more accurately. Performance of the two final multivariable models (one for OS and one for PFS) was assessed with Harrell's concordance-index (C-index)[21], which estimates the probability of concordance between predicted and observed responses. Finally, internal validation of the models was carried out by comparing the C-indices of 1000 bootstrap replications to correct for optimism[22].

Lastly, these steps were repeated in subgroups of patients, both for the subgroup with data on AEDs and corticosteroids, and for the subgroup with data on the molecular markers. Analyses were performed using IBM SPSS, version 23.0[23], while the calculation of C-indices and the validation of the models were performed with R[24] using the rms package[25].

Results

Individual patient data were obtained from 15 international RCTs including a total of 6048 patients (range 81-921 patients). The date of randomization ranged from 1996 to 2015 (supplementary Table 1).

Data collection and baseline characteristics

Sociodemographic and clinical characteristics of the patients included in the RCTs are summarized in Table 1. Baseline HRQoL data were available for 86% (5217/6084) of the patients. Patients who completed a baseline HRQoL questionnaire were younger (mean age 53 versus 55 years), had a better WHO PS (WHO=0 in 38% versus 29%) and had undergone resection more often (74% versus 62%) than patients who did not complete the baseline HRQoL assessment. There was also a significant difference in survival time: patients who completed a HRQoL baseline form had longer OS than patients without a baseline form (median 18.0 months, 95% CI [17.3-18.7] versus median 14.7 months, 95% CI [13.3-16.1], p<.001). Similarly for PFS, patients with a baseline form had longer PFS than patients without a baseline form (8.3 months, 95% CI [7.9-8.7] versus 5.3 months, 95% CI [4.7-5.9], p<.001).

Univariable analyses

Results of the univariable analyses showed that female sex, a younger age, non-glioblastoma tumor type, a better WHO PS, newly diagnosed tumor type, resection and treatment with radiotherapy alone were associated with longer OS and PFS (Table 2). Moreover, better scores on all baseline HRQoL functioning scales were associated with longer OS and PFS, except for emotional functioning, which was not significantly associated with longer PFS. Furthermore, lower baseline scores on most symptoms scales were associated with longer OS and PFS, except for pain, insomnia, diarrhea, headache, seizures and itchy skin that were not prognostic for either OS or PFS, and hair loss not for PFS (Table 2).

Clinical model

In the multivariable models for OS and PFS including the clinical variables only, female sex, a younger age, non-glioblastoma tumor type, a better WHO PS, resection, and allocated treatment other than

radiotherapy alone were independently associated with a longer OS and PFS (Table 3 and Table 4 respectively).

Clinical and HRQoL model

In the multivariable models including both the clinical and HRQoL variables, all clinical variables remained significantly prognostic for OS and PFS. Among the HRQoL variables, better role and cognitive functioning and less motor dysfunction were associated with longer OS (Table 3), and better cognitive functioning, less nausea and vomiting and more appetite loss were associated with longer PFS.

Predictive accuracy

The validated C-index for the model predicting OS with both the clinical and HRQoL variables was reasonable, and similar in predicting survival to the model with the clinical variables only (C=.721 versus C=.716, respectively) (Table 5). This represents a relative gain in predictive accuracy of 1.1% (see Table 5 for the calculation). Similar results were found for PFS, with predictive abilities of C=.683 and C=.679 for the clinical model and clinical + HRQoL model, respectively. The added value of the HRQoL scales in this model was also small (0.7%, Table 5).

Subgroup analysis: AEDs and corticosteroids

Baseline data on AEDs and corticosteroid use were available for 48% of the patients. Besides the clinical variables, only the none-use of corticosteroids at baseline was found to be prognostic for longer OS in both the clinical and clinical + HRQoL model, whereas the (none-)use of AEDs was not (supplementary table 2). Among the HRQoL variables, lower levels of fatigue and motor dysfunction were prognostic for longer OS and better role functioning, less appetite loss and weakness of the legs were prognostic for longer PFS (supplementary table 2). The added value of HRQoL variables in the

presence of the clinical variables and AEDs and corticosteroid use after validation was small: 0.5% for OS and -0.2% for PFS, with similar C-indices as for the 'original model'(Table 5).

Subgroup analysis: WHO 2016 classification and MGMT status

When constructing a model including the WHO 2016 tumor classification and MGMT status, 35% of patients (maximum n=1748) were available for the analysis. In the model with both the clinical and HRQoL variables, female sex, younger age, a better WHO PS, MGMT-methylation, worse emotional functioning, less fatigue, and less nausea and vomiting were prognostic for longer OS (supplementary table 3). For PFS, the same clinical variables except sex were prognostic for longer PFS, and among the HRQoL variables only less nausea and vomiting was prognostic for longer PFS. Results of this subgroup analysis also showed a small added value of the HRQoL variables compared to the clinical variables only; 1.8% for OS and 0.7% for PFS (Table 5).

Discussion

We studied the added value of baseline HRQoL as prognostic indicator for OS and PFS in a large, heterogeneous sample of glioma patients by pooling individual HRQoL and sociodemographic/clinical data from previously conducted RCTs, controlling for known prognostic factors. Although this sample represents a large proportion of the glioma patient population regarding sex, age and type of tumor, the patients included in our analysis had a relatively good performance status, indicating selection bias, likely driven by stringent inclusion criteria for RCTs[26]. Moreover, patients who completed a baseline form (86%) had a better OS and PFS than those who did not, reflecting a selection bias in the available sample of trial patients.

The prognostic value of known clinical parameters was confirmed in this study; younger and female patients, those with a better performance status, a non-glioblastoma tumor type (irrespective of further tumor histology), and patients who underwent resection and were treated with other

treatment regimens than radiotherapy alone had both significantly longer OS and PFS. Of note, we did not include interaction effects, hampering estimation of survival for specific subgroups (e.g. glioblastoma patients who were treated with radiotherapy only). Nevertheless, several HRQoL parameters provided independent prognostic information in addition to the known clinical variables, confirming previous results in glioma patients[8-10]. Although the C-index scores indicated that adding HRQoL parameters to the prognostic model did improve the model, the added value was small (1.1% for OS and 0.7% for PFS). Overall, the predictive accuracy was reasonable for OS (C-index of .716), and slightly less accurate for PFS (c-index of .679). Because HRQoL added little prognostic information to the clinical variables, further validation and calibration of these models was not considered meaningful.

Role and cognitive functioning were the only two HRQoL variables that were independently prognostic for both OS and PFS. Other studies including different types of glioma patients also found that baseline cognitive complaints, as measured with the EORTC QLQ-C30 cognitive functioning scale, or objective cognitive functioning measured with a neuropsychological test battery or the Mini-Mental State Examination (MMSE), were prognostic for OS[8,9,27-31]. Cognitive impairment might be an early indicator of tumor progression which may not (yet) be visible or detected on scans[32]. Another explanation could be that patients' cognitive complaints act as a proxy for tumor volume, which was not included as a covariate in our study, but is associated with survival[33]. The finding that role functioning was an independent prognostic variable for OS did not replicate earlier brain tumor studies, but might be indicative of the impact of the disease on functioning in daily life. Indeed, role functioning was also found to be prognostic in, for example, testicular cancer patients, where the disease similarly strikes at a younger age compared to other cancers, affecting the working life of patients, and therefore the role functioning of these patients[6]. Other HRQoL variables that were prognostic in our study were motor dysfunction (for OS), nausea and vomiting and appetite loss (for PFS). These symptoms may be an indicator of the severity of the disease.

In the two subgroup analyses including AEDs and corticosteroid use or the molecular markers, all known clinical variables remained prognostic for OS and PFS. In contrast, the HRQoL variables varied across subgroups: other functioning scales and symptoms were of prognostic value in the subgroup models when compared to the 'original model'. Moreover, some HRQoL variables were unexpectedly prognostic for PFS and OS, i.e. more appetite loss for prolonged PFS in the main analysis and worse emotional functioning for prolonged OS in the subanalysis including the molecular markers. These findings imply that although the clinical variables appeared to be robust prognostic markers, the prognostic value of the HRQoL variables depended on the subgroup of patients included. For the subgroup analysis including the molecular markers, assessment period may also be a factor, as the patients for whom data on molecular markers were available were included in more recent RCTs. We also considered using the HRQoL summary score[34] instead of all individual scales/items, however, the summary score consists of items of the EORTC QLQ-C30 only, and does not include the brain tumor specific items/scales included in the EORTC QLQ-BN20. Taken together, our results suggest that the role of HRQoL data in predicting prognosis is limited, and not useful for stratification in future clinical trials, as it is unclear which variables should be assessed and included.

Although the added prognostic value of HRQoL was small, HRQoL remains an important outcome in both clinical trials and practice. In clinical trials, HRQoL assessment is important to determine the net clinical benefit of a new treatment strategy[35]. In clinical practice, HRQoL assessments are important in monitoring patients' functioning over time, and in informing patients and clinicians about the effect of the tumor and treatment on symptoms, functioning and quality of life. In addition, rather than baseline HRQoL data, a change in HRQoL from baseline during treatment, reflecting the impact of treatment on HRQoL, may be of more prognostic value, and should be further investigated to inform patients in clinical practice on the impact of treatment[36].

In conclusion, this study investigated the added prognostic value of HRQoL to the known clinical variables in a large heterogeneous sample of glioma patients. Although some HRQoL

parameters were independently prognostic for survival, the added value of baseline HRQoL to the known clinical prognostic variables was small. Thus, although HRQoL has proven to be an important outcome in glioma patients for various purposes, HRQoL adds little for prognostic purposes.

References

1. Aaronson NK, Taphoorn MJ, Heimans JJ, et al. Compromised health-related quality of life in patients with low-grade glioma. *Journal of Clinical Oncology.* 2011; 29(33):4430-4435.

2. Dirven L, Aaronson NK, Heimans JJ, Taphoorn M. Health-related quality of life in high-grade glioma patients. *Chin J Cancer.* 2014; 33(1):40-45.

3. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2011-2015. *Neuro Oncol.* 2018; 20(suppl_4):iv1-iv86.

4. Efficace F, Biganzoli L, Piccart M, et al. Baseline health-related quality-of-life data as prognostic factors in a phase III multicentre study of women with metastatic breast cancer. *European Journal of Cancer.* 2004; 40(7):1021-1030.

5. Maisey N, Norman A, Watson M, Allen M, Hill M, Cunningham D. Baseline quality of life predicts survival in patients with advanced colorectal cancer. *European Journal of Cancer.* 2002; 38(10):1351-1357.

6. Quinten C, Martinelli F, Coens C, et al. A global analysis of multitrial data investigating quality of life and symptoms as prognostic factors for survival in different tumor sites. *Cancer.* 2014; 120(2):302-311.

7. Gotay CC, Kawamoto CT, Bottomley A, Efficace F. The prognostic significance of patient-reported outcomes in cancer clinical trials. *J Clin Oncol.* 2008; 26(8):1355-1363.

8. Mauer M, Stupp R, Taphoorn M, et al. The prognostic value of health-related quality-of-life data in predicting survival in glioblastoma cancer patients: results from an

international randomised phase III EORTC Brain Tumour and Radiation Oncology Groups, and NCIC Clinical Trials Group study. *British journal of cancer.* 2007; 97(3):302-307.

9. Mauer ME, Taphoorn MJ, Bottomley A, et al. Prognostic value of health-related quality-of-life data in predicting survival in patients with anaplastic oligodendrogliomas, from a phase III EORTC brain cancer group study. *Journal of Clinical Oncology.* 2007; 25(36):5731-5737.

10. Paquette B, Vernerey D, Chauffert B, et al. Prognostic value of health-related quality of life for death risk stratification in patients with unresectable glioblastoma. *Cancer medicine.* 2016; 5(8):1753-1764.

11. Lamborn KR, Yung WA, Chang SM, et al. Progression-free survival: an important end point in evaluating therapy for recurrent high-grade gliomas. *Neuro-oncology.* 2008; 10(2):162-170.

12. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta neuropathologica.* 2016; 131(6):803-820.

13. Weller M, Felsberg J, Hartmann C, et al. Molecular predictors of progression-free and overall survival in patients with newly diagnosed glioblastoma: a prospective translational study of the German Glioma Network. *Journal of Clinical Oncology.* 2009; 27(34):5743-5750.

14. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *Journal of the national cancer institute.* 1993; 85(5):365-376.

15. Taphoorn MJ, Claassens L, Aaronson NK, et al. An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients. *European Journal of Cancer.* 2010; 46(6):1033-1040.

16. Osoba D, Aaronson N, Muller M, et al. The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer-specific questionnaires. *Quality of Life Research.* 1996; 5(1):139-150.

17. Fayers PM, Aaronson NK, Bjordal K, Curran D, Grønvold M. EORTC QLQ-C30 scoring manual, 3rd edn. 2001.

18. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *Journal of Clinical Oncology*. 2010; 28(11):1963-1972.

19. Macdonald DR, Cascino TL, Schold Jr SC, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *Journal of Clinical Oncology.* 1990; 8(7):1277-1280.

20. Kirkwood BR, Sterne JA. *Essential medical statistics*: John Wiley & Sons; 2010.

21. Harrell FE, Lee KL, Mark DB. Tutorial in biostatistics multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Statistics in medicine.* 1996; 15:361-387.

22. Sauerbrei W, Schumacher M. A bootstrap resampling procedure for model building: application to the Cox regression model. *Statistics in medicine.* 1992; 11(16):2093-2109.

23. Released I. IBM SPSS Statistics for Windows. 20. *Armonk, NY: IBM Corp.* 2013.

24. Team RC. R: A language and environment for statistical computing. 2013.

25. Harrell Jr FE. rms: Regression Modeling Strategies. R package version 4.0-0. *City.* 2013.

26. Dirven L, Reijneveld JC, Aaronson NK, Bottomley A, Uitdehaag BM, Taphoorn MJ. Health-related quality of life in patients with brain tumors: limitations and additional outcome measures. *Current neurology and neuroscience reports.* 2013; 13(7):359.

27. Klein M, Postma T, Taphoorn M, et al. The prognostic value of cognitive functioning in the survival of patients with high-grade glioma. *Neurology.* 2003; 61(12):1796-1798.

28. Meyers CA, Hess KR, Yung WA, Levin VA. Cognitive function as a predictor of survival in patients with recurrent malignant glioma. *Journal of Clinical Oncology.* 2000; 18(3):646-646.

29. Johnson DR, Sawyer AM, Meyers CA, O'neill BP, Wefel JS. Early measures of cognitive function predict survival in patients with newly diagnosed glioblastoma. *Neuro-oncology.* 2012; 14(6):808-816.

30. Brown PD, Buckner JC, O'Fallon JR, et al. Importance of baseline mini-mental state examination as a prognostic factor for patients with low-grade glioma. *International Journal of Radiation Oncology* Biology* Physics.* 2004; 59(1):117-125.

31. Gorlia T, van den Bent MJ, Hegi ME, et al. Nomograms for predicting survival of patients with newly diagnosed glioblastoma: prognostic factor analysis of EORTC and NCIC trial 26981-22981/CE. 3. *The lancet oncology.* 2008; 9(1):29-38.

32. Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. *The Lancet. Neurology.* 2004; 3(3):159-168.

33. Kreth FW, Faist M, Rossner R, Volk B, Ostertag CB. Supratentorial World Health Organization grade 2 astrocytomas and oligoastrocytomas: a new pattern of prognostic factors. *Cancer.* 1997; 79(2):370-379.

34. Giesinger JM, Kieffer JM, Fayers PM, et al. Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. *Journal of clinical epidemiology.* 2016; 69:79-88.

35. Dirven L, Armstrong TS, Taphoorn MJ. Health-related quality of life and other clinical outcome assessments in brain tumor patients: challenges in the design, conduct and interpretation of clinical trials. *Neurooncol Pract.* 2015; 2(1):2-5.

36. Beer TM, Miller K, Tombal B, et al. The association between health-related quality-of-life scores and clinical outcomes in metastatic castration-resistant prostate cancer patients: Exploratory analyses of AFFIRM and PREVAIL studies. *Eur J Cancer.* 2017; 87:21-29.

Table 1. Baseline sociodemographic and clinical characteristics of the patients included in the RCTs, separately for those with and without completed baseline health-related quality of life forms

	All patients n=6084	**HRQoL present n=5217**	**HRQoL absent n=867**	**P-value**
	n (%)	n (%)	n (%)	
Sex				.165
Male	3710 (61)	3211 (62)	499 (58)	
Female	2351 (39)	2005 (38)	346 (40)	
Missing	23 (0)	1 (0)	22 (3)	
Age (mean, SD)	53 (13)	53 (13)	55 (13)	<.001*
Histology				.423
Non-glioblastoma	1762 (29)	1501 (29)	261 (30)	
Glioblastoma	4322 (71)	3716 (71)	606 (70)	
Disease stage				<.001*
Newly diagnosed	4968 (82)	4330 (83)	638 (74)	
Recurrent	1116 (18)	887 (17)	229 (26)	
WHO PS				<.001*
WHO 0	2257 (37)	2006 (38)	251 (29)	
WHO 1	3015 (50)	2587 (50)	428 (49)	
WHO 2	756 (12)	604 (12)	152 (18)	
Missing	56 (1)	20 (0)	36 (4)	
Allocated treatment				<.001*
RT alone	1349 (22)	1105 (21)	244 (28)	
Chemo alone	1107 (18)	840 (16)	267 (31)	
Angio alone	126 (2)	106 (2)	20 (2)	
RT and chemo	1633 (27)	1455 (28)	178 (21)	
RT and chemo and angio	834 (14)	807 (15)	27 (3)	
Chemo and angio	444 (7)	360 (7)	84 (10)	
TTF alone	120 (2)	107 (2)	13 (2)	
Chemo and TTFields	466 (8)	434 (8)	32 (4)	
Missing	5 (0)	3 (0)	2 (0)	
Surgical status				<.001*
Resected	4379 (72)	3845 (74)	534 (62)	
Not resected	1523 (25)	1221 (23)	302 (35)	
Missing	182 (3)	151 (3)	31 (4)	
Use of AEDs				.033*
No	1337 (22)	1134 (22)	203 (23)	
Yes	1566 (26)	1371 (26)	195 (23)	
Missing	3181 (52)	2712 (52)	469 (54)	
Use of steroids				.807
No	3182 (52)	2754 (53)	428 (49)	
Yes	2329 (38)	2021 (39)	308 (36)	
Missing	573 (9)	442 (9)	131 (15)	
IDH status				<.001*
IDH-mutant	463 (8)	396 (8)	67 (8)	
IDH-wildtype	875 (14)	804 (15)	71 (8)	

Missing	4746 (78)	4017 (77)	729 (84)	
1p/19q status				<.001*
Codeleted	214 (4)	175 (3)	39 (4)	
Non-codeleted	1485 (24)	1338 (26)	147 (17)	
Missing	4385 (73)	3704 (71)	681 (79)	
MGMT status				<.001*
Methylated	1657 (27)	1483 (28)	174 (20)	
Unmethylated	1634 (27)	1462 (28)	172 (20)	
Missing	2783 (46)	2272 (44)	521 (60)	

WHO PS, World Health Organisation Performance Status; Trt, allocated treatment; RT, radiotherapy; chemo, chemotherapy; Angio, angiogenesis inhibitor; TTF, tumor-treating fields; HRQoL, health-Related Quality of Life; IDH, isocitrate dehydrogenase mutations; MGMT, O^6-methylguanine-DNA methyltransferase promotor methylation

Table 2. Univariable results of Cox proportional hazard models for overall and progression-free survival for the clinical variables and health-related quality of life parameters

	Overall survival (OS)		Progression-free survival (PFS)	
	HR death (95% CI)[a]	P-value	HR progression (95% CI)[a]	P-value
Clinical variables				
Female (ref)	ref		ref	
Male	1.19 (1.10-1.28)	<.001*	1.18 (1.10-1.25)	<.001*
Age [c]	1.04 (1.04-1.04)	<.001*	1.03 (1.02-1.03)	<.001*
Non-glioblastoma (ref)	ref		ref	
Glioblastoma	2.95 (2.68-3.25)	<.001*	2.80 (2.59-3.03)	<.001*
WHO PS 0 (ref)	ref		ref	
WHO PS 1	1.64 (1.52-1.78)	<.001*	1.49 (1.39-1.59)	<.001*
WHO PS 2	3.05 (2.73-3.41)	<.001*	2.17 (1.95-2.41)	<.001*
Resected (ref)	ref		ref	
Not resected	1.75 (1.60-1.92)	<.001*	1.54 (1.43-1.66)	<.001*
Newly diagnosed (ref)	ref		ref	
Recurrent	2.45 (2.21-2.70)	<.001*	2.87 (2.65-3.11)	<.001*
Trt: RT alone (ref)	ref		ref	
Trt: Chemo alone	1.61 (1.43-1.83)	<.001*	1.99 (1.79-2.21)	<.001*
Trt: Angio alone	2.70 (2.05-3.55)	<.001*	4.22 (3.42-5.20)	<.001*
Trt: RT and chemo	.91 (.82-1.00)	.060	1.13 (1.03-1.25)	.013
Trt: RT and chemo and angio	1.05 (.94-1.19)	.386	1.18 (1.06-1.32)	.003*
Trt: Chemo and angio	1.94 (1.62-2.32)	<.001*	2.76 (2.41-3.16)	<.001*
Trt: TTF alone	4.00 (3.22-4.98)	<.001*	4.16 (3.33-5.19)	<.001*
Trt: Chemo and TTFields	1.07 (.93-1.22)	.370	2.17 (1.81-2.45)	<.001*
HRQoL – QLQ-C30				
Global Health status [c]	.991 (.989-.992)	<.001*	.995 (.993-.996)	<.001*
Physical functioning [c]	.989 (.987-.990)	<.001*	.993 (.991-.994)	<.001*
Role functioning [c]	.994 (.993-.995)	<.001*	.997 (.996-.998)	<.001*
Emotional functioning [c]	.997 (.995-.998)	<.001*	1.000 (.999-1.001)	.793
Cognitive functioning [c]	.992 (.991-.994)	<.001*	.996 (.994-.997)	<.001*
Social functioning [c]	.996 (.995-.998)	<.001*	.998 (.997-1.000)	.004*
Fatigue [c]	1.006 (1.005-1.008)	<.001*	1.004 (1.002-1.005)	<.001*
Nausea and vomiting [c]	1.004 (1.001-1.007)	.006*	1.005 (1.002-1.007)	<.001*
Pain [c]	1.000 (.999-1.002)	.739	.999 (.998-1.001)	.257
Dyspnea [c]	1.002 (1.001-1.004)	.006*	1.001 (1.000-1.003)	.097
Insomnia [c]	1.000 (.999-1.001)	.651	1.000 (.998-1.001)	.420
Appetite loss [c]	1.002 (1.001-1.004)	.006*	1.002 (1.001-1.004)	.004*
Constipation [c]	1.002 (1.001-1.003)	.004*	1.002 (1.001-1.003)	.004*
Financial difficulties [c]	.999 (.997-1.000)	.015*	.998 (.997-.999)	.002*
Diarrhea [c]	1.000 (.998-1.003)	.765	.999 (.997-1.001)	.235
HRQoL – QLQ-BN20				
Future uncertainty [c]	1.005 (1.003-1.006)	<.001*	1.003 (1.002-1.004)	<.001*

Visual disorder [c]	1.006 (1.004-1.008)	<.001*	1.005 (1.003-1.006)	<.001*
Motor dysfunction [c]	1.010 (1.009-1.012)	<.001*	1.006 (1.005-1.008)	<.001*
Communication deficit [c]	1.006 (1.005-1.007)	<.001*	1.004 (1.003-1.005)	<.001*
Headache [c]	.999 (.998-1.001)	.352	.999 (.998-1.000)	.103
Seizures [c]	1.001 (.999-1.003)	.270	.999 (.998-1.001)	.437
Drowsiness [c]	1.002 (1.002-1.005)	<.001*	1.003 (1.002-1.004)	<.001*
Hair loss [c]	.998 (.997-1.000)	.027*	.999 (.998-1.001)	.301
Itchy skin [c]	.999 (.997-1.001)	.224	.999 (.998-1.001)	.355
Weakness of legs [c]	1.006 (1.005-1.008)	<.001*	1.003 (1.002-1.004)	<.001*
Bladder control [c]	1.006 (1.005-1.008)	<.001*	1.003 (1.002-1.005)	<.001*

OS, overall survival; PFS, progression free survival; HR, Hazard ratio; CI, confidence interval; WHO PS, World Health Organisation Performance Status; Trt, allocated treatment; RT, radiotherapy; chemo, chemotherapy; Angio, angiogenesis inhibitor; TTF, tumor-treating fields; HRQoL QLQ-C-30, health-related quality of life questionnaire QOL-C30; HRQoL – QLQ-BN20, health-related quality of life questionnaire brain tumor module; [c] continues variable; *statistically significant.

[a] HRs reflect the probability for the event: death in case of OS and progression in case of PFS. HRs of >1 suggest and increased risk of death/progression compared to the reference category, HRs <1 suggest a smaller risk.

Table 3. Multivariable Cox proportional hazard models for overall survival, one including clinical data only, and one model including both clinical and HRQoL data

	Cox model for clinical data		Cox model for clinical and HRQOL data	
	HR death (95% CI)[a]	**P-value[a]**	**HR death (95% CI) [a]**	**P-value[a]**
Clinical variables				
Female (ref)	ref		ref	
Male	1.22 (1.13-1.31)	<.001*	1.28 (1.18-1.39)	<.001*
Age[c]	1.03 (1.02-1.03)	<.001*	1.03 (1.02-1.03)	<.001*
Non-glioblastoma (ref)	ref		ref	
Glioblastoma	3.44 (3.01-3.90)	<.001*	3.65 (3.17-4.13)	<.001*
WHO PS 0 (ref)	ref		ref	
WHO PS 1	1.37 (1.26-1.49)	<.001*	1.29 (1.18-1.42)	<.001*
WHO PS 2	2.00 (1.78-2.26)	<.001*	1.62 (1.41-1.87)	<.001*
Resected (ref)	ref		ref	
Not resected	1.46 (1.32-1.61)	<.001*	1.48 (1.33-1.64)	<.001*
Trt: RT alone (ref)	ref		ref	
Trt: Chemo alone	.65 (.56-.76)	<.001*	.67 (.57-.79)	<.001*
Trt: Angio alone	.50 (.35-.71)	<.001*	.48 (.33-.69)	<.001*
Trt: RT and chemo	.64 (.57-.71)	<.001*	.62 (.55-.70)	<.001*
Trt: RT and chemo and angio	.50 (.44-.57)	<.001*	.50 (.44-.68)	<.001*
Trt: Chemo and angio	.40 (.30-.55)	<.001*	.37 (.27-.51)	<.001*
Trt: TTF alone	.79 (.58-1.07)	.132	.75 (.55-1.04)	.083*
Trt: Chemo and TTFields	.45 (.39-.52)	<.001*	.47 (.40-.55)	<.001*
HRQoL variables				
Role functioning[c]	-	-	.99 (.99-.99)	.037*
Cognitive functioning[c]	-	-	.99 (.99-.99)	.002*
Motor dysfynction[c]	-	-	1.00 (1.00-1.01)	.026*

HR, Hazard ratio; CI, confidence interval; WHO PS, World Health Organisation Performance Status; Trt, allocated treatment; RT, radiotherapy; chemo, chemotherapy; Angio, angiogenesis inhibitor; TTF, tumor-treating fields; HRQoL, health-related quality of life; ref, reference group in analysis; [a] significant HRQoL variables are presented; [c] continues variable; * statistically significant.
Models are stratified for disease stage (newly diagnosed/recurrent).
[a] HRs reflect the probability for the event death. HRs of >1 suggest and increased risk of death compared to the reference category, HRs <1 suggest a smaller risk.

Table 4. Multivariable Cox proportional hazard models for progression-free survival, one including clinical data only, and one model including both clinical and HRQoL data

	Cox model for clinical data		Cox model for clinical and HRQOL data	
	HR progression (95% CI) [a]	**P-value**[a]	**HR progression (95% CI)** [a]	**P-value**[a]
Clinical variables				
Female (ref)	ref		ref	
Male	1.18 (1.11-1.26)	<.001*	1.19 (1.11-1.27)	<.001*
Age[c]	1.01 (1.01-1.01)	<.001*	1.01 (1.01-1.01)	<.001*
Non-glioblastoma (ref)	ref		ref	
Glioblastoma	3.23 (2.90-3.60)	<.001*	3.29 (2.93-3.69)	<.001*
WHO PS 0 (ref)	ref		ref	
WHO PS 1	1.25 (1.16-1.34)	<.001*	1.22 (1.13-1.32)	<.001*
WHO PS 2	1.40 (1.25-1.57)	<.001*	1.28(1.13-1.45)	<.001*
Resected (ref)	ref		ref	
Not resected	1.67 (1.07-1.27)	.001*	1.14 (1.04-1.25)	.004*
Trt: RT alone (ref)	ref		ref	
Trt: Chemo alone	1.06 (.93-1.20)	.396	1.14 (1.00-1.30)	.059
Trt: Angio alone	.70 (.53-.92)	.009*	.72 (.55-.95)	.020*
Trt: RT and chemo	.70 (.63-.78)	<.001*	.73 (.65-.82)	<.001*
Trt: RT and chemo and angio	.50 (.44-.56)	<.001*	.52 (.45-.59)	<.001*
Trt: Chemo and angio	.56 (.45-.70)	<.001*	.58 (.46-.74)	<.001*
Trt: TTF alone	.70 (.53-.93)	.015*	.72 (.54-.96)	.027*
Trt: Chemo and TTFields	.92 (.80-1.06)	.245	.99 (.86-1.15)	.894
HRQoL variables				
Role functioning[c]	-	-	.99 (.99-.99)	.010*
Cognitive functioning[c]	-	-	.99 (.99-.99)	.032*
Nausea and Vomiting[c]	-	-	1.00 (1.00-1.01)	.010*
Appetite loss[c]	-	-	.99 (.99-.99)	.011*

HR, Hazard ratio; CI, confidence interval; WHO PS, World Health Organisation Performance Status; Trt, allocated treatment; RT, radiotherapy; chemo, chemotherapy; Angio, angiogenesis inhibitor; TTF, tumor-treating fields; HRQoL, health-related quality of life; Ref, reference group in analysis; [a] significant HRQoL variables are presented; [c] continues variable; * statistically significant.
Models are stratified for disease stage (newly diagnosed/recurrent).
[a] HRs reflect the probability for the event progression. HRs of >1 suggest and increased risk of progression compared to the reference category, HRs <1 suggest a smaller risk.

Table 5. Performance and internal validation of the multivariable Cox proportional hazard models for overall survival (OS) and progression-free survival (PFS)

Model	n	c-index	Bootstrapped c-index (mean from 1000 bootstraps)	Optimism[a] (%)	Added value[b] (%)
Main analysis					
OS: clinical model	4944	.7172	.7157	.002	-
OS: clinical + HRQoL model	4396	.7254	.7213	.004	1.1%
PFS: clinical model	5018	.6805	.6793	.001	-
PFS: clinical + HRQoL model	4458	.6863	.6828	.004	0.7 %
Sub analysis					
OS: clinical model + AEDs, steroids	2292	.7069	.7028	.004	-
OS: clinical + HRQoL model + AEDs, steroids	2069	.7166	.7054	.011	0.5%
PFS: clinical model + AEDs, steroids	2321	.7058	.7032	.003	-
PFS: clinical + HRQoL model + AEDs, steroids	2093	.7099	.7021	.008	-.2%
OS: WHO 2016 classification + MGMT: clinical model	1748	.6962	.6877	.009	-
OS: WHO 2016 classification + MGMT: clinical + HRQoL model	1503	.7142	.6970	.017	1.8%
PFS: WHO 2016 classification + MGMT: clinical model	1765	.6865	.6800	.007	-
PFS: WHO 2016 classification + MGMT: clinical + HRQoL model	1518	.6979	.6835	.014	0.7%

OS, overall survival; PFS, progression free survival; AEDs, anti-epileptic drugs; HRQoL, health-related quality of life; WHO, World Health Organisation; [a] measure of internal validation: c-index minus the bootstrapped c-index; [b] added value of the bootstrapped c-index of the clinical + HRQoL model compared to the clinical mode. The added value is calculated using the formula: ((clinical+HRQoL model– 0.5)/(0.5)(*100)- (clinical model– 0.5)/(0.5)(*100)).

Supplementary Table 1. Included RCTs

Included RCTs	Patient population	Study sample size of RCT	ref
EORTC 26951	Newly diagnosed anaplastic oligodendroglioma	292	1
EORTC 22981-26981	Newly diagnosed glioblastoma	573	2
EORTC 26071 (CENTRIC)	Newly diagnosed glioblastoma MGMT methylated	504	3
EORTC 22033-26033	Newly diagnosed and recurrent low-grade glioma	700	4
EORTC 26101	Recurrent glioblastoma	592	5
EORTC 26091 (TAVAREC)	Recurrent grade II and III gliomas	155	6
EORTC 26053-22054 (CATNON)	non-1p/191 deleted anaplastic glioma	745	7
NOA-08	Grade III and IV astrocytoma in elderly	373	8
NORDIC	Newly diagnosed glioblastoma in elderly	342	9
ANOCEF	Newly diagnosed glioblastoma in elderly	81	10
BELOB	Recurrent glioblastoma	148	11
AVAGLIO	Newly diagnosed glioblastoma	921	12
GLARIUS	Newly diagnosed MGMT-non methylated glioblastoma	170	13
EF-11	Recurrent glioblastoma	237	14
EF-14	Newly diagnosed glioblastoma	700	15

Supplementary Table 2. Subgroup analysis: Multivariable Cox proportional hazard models for overall survival and progression-free survival including clinical and HRQoL data, and anti-epileptic drug and steroid use

	Overall survival (OS)		Progression-free survival (PFS)	
	HR death (95% CI)[a]	**P-value[a]**	**HR progression (95% CI)[a]**	**P-value[a]**
Clinical variables				
Female (ref)	ref			
Male	1.2 (1.1-1.4)	.001*	NS	NS
Age[c]	1.0 (1.0-1.3)	<.001*	NS	NS
Non-glioblastoma (ref)	ref		ref	
Glioblastoma	16.5 (8.0-34.3)	<.001*	5.3 (4.2-6.6)	<.001*
WHO PS 0 (ref)	ref		ref	
WHO PS 1	1.2 (1.0-1.3)	.051*	1.1 (1.0-1.3)	.024*
WHO PS 2	1.5 (1.2-1.9)	<.001*	1.3 (1.0-1.5)	.030*
Trt: RT alone	ref		ref	
Trt: Chemo alone	.36 (.3-.5)	<.001*	1.1 (.8-.1.3)	.666
Trt: Angio alone	.30 (.2-.5)	<.001*	.68 (.5-.9)	.018*
Trt: RT and chemo	.18 (.1-.3)	<.001*	.31 (.2-.4)	<.001*
Trt: RT and chemo and angio	.17 (.1-.3)	<.001*	.28 (.2-.4)	<.001*
Trt: Chemo and angio	.23 (.1-.4)	<.001*	.54 (.4-.7)	<.001*
Trt: TTF alone	.40 (.3-.6)	<.001*	.67 (.5-.9)	.019*
Trt: Chemo and TTFields	.24 (.2-.4)	<.001*	.72 (.6-.9)	.008*
Steroids use: no (ref)	ref			
Steroids use: yes	.79 (.7-.9)	<.001*	NS	NS
HRQoL variables				
Fatigue[c]	1.0 (1.0-1.0)	.023*	NS	NS
Motor dysfunction[c]	1.0 (1.0-1.0)	<.001*	NS	NS
Role functioning[c]	NS	NS	.99 (.99-.99)	.009*
Appetite loss[c]	NS	NS	.10 (.10-.10)	.003*
Weakness of the legs[c]	NS	NS	.10 (.10-.10)	.034*

HR, Hazard ratio; CI, confidence interval; WHO PS, World Health Organisation Performance Status; Trt, allocated treatment; RT, radiotherapy; chemo, chemotherapy; Angio, angiogenesis inhibitor; TTF, tumor-treating fields; HRQoL, health-related quality of life; Ref, reference group in analysis; [a] significant HRQoL variables are presented; [c] continues variable; * statistically significant; NS, non-significant; Models are stratified for disease stage (newly diagnosed/recurrent).

[a] HRs reflect the probability for the event: death in case of OS and progression in case of PFS. HRs of >1 suggest and increased risk of death/progression compared to the reference category, HRs <1 suggest a smaller risk.

Supplementary Table 3. Subgroup analysis: Multivariable Cox proportional hazard models for overall survival and progression-free survival including clinical and HRQoL data, with tumor classification based on the WHO 2016 classification criteria

	Overall survival (OS)		Progression-free survival (PFS)	
	HR death (95% CI)[a]	P-value[a]	HR progression (95% CI)[a]	P-value[a]
Clinical variables				
Female (ref)	ref		ref	
Male	1.27 (1.10-1.47)	.002*	NS	NS
Age[c]	1.02 (1.02-1.03)	<.001*	1.01 (1.00-1.01)	.019*
Diffuse Astrocytoma IDH-mutant (ref)	ref		ref	
Diffuse astrocytoma IDH-wildtype	2.18 (.30-15.69)	.383	1.60 (.94—2.72)	.084
Diffuse astrocytoma NOS	3.30 (.46-23.50)	.233	1.41 (.83-2.43)	.203
Anaplastic astrocytoma IDH-mutant	2.04 (.46-8.98)	.348	.43 (.24-.76)	.004*
Anaplastic astrocytoma IDH-wildtype	6.28 (1.46-27.08)	.014*	2.16 (1.33-3.51)	.002*
Anaplastic astrocytoma NOS	2.94 (.69-12.53)	.145	.86 (.55-1.35)	.511
Glioblastoma IDH-mutant	5.35 (1.21-23.70)	.027*	2.53 (1.51-4.23)	<.001*
Glioblastoma IDH-wildtype	12.29 (2.98-.50.65)	.001*	4.29 (2.92-6.29)	<.001*
Glioblastoma NOS	9.23 (2.22-38.40)	.002*	3.53 (2.34-5.32)	<.001*
Oligodendroglioma IDH mutant and p19q-codeleted	.00 (.00-4.4E71)	.918	.88 (.54-1.45)	.623
Oligodendroglioma NOS	.00 (.00-1.4E101)	.938	1.37 (.81-2.32)	.239
Oligoastrocytoma NOS	.52 (.05-5.79)	.597	1.03 (.69-1.52)	.904
Anaplastic oligoastrocytoma NOS	4.24 (1.02-17.72)	.048*	1.23 (.84-1.82)	.288
WHO PS 0 (ref)	ref		ref	
WHO PS 1	1.18 (1.01-1.39)	<.001*	1.15 (1.01-1.32)	.034*
WHO PS 2	1.76 (1.33-2.23)	<.001*	1.57 (1.22-2.01)	<.001*
Resected (ref)	ref		ref	
Not resected	1.75 (1.39-2.19)	<.001*	1.21 (1.00-1.45)	.047*
Trt: RT alone (ref)	ref		ref	
Trt: Chemo alone	.85 (.56-1.31)	.468	1.35 (1.05-1.72)	.018*
Trt: Angio alone	.95 (.52-1.74)	.868	.87 (.52-1.43)	.577
Trt: RT and chemo	.86 (.65-1.13)	.276	.74 (.59-.93)	.009*
Trt: RT and chemo and angio	.79 (.55-1.13)	.198	.61 (.45-.81)	.001*
Trt: Chemo and angio	.50 (.27-.94)	.030*	.42 (.25-.72)	.002*
Trt: Chemo and TTFields	.54 (.36-.82)	.003*	1.12 (.83-1.5)	.464
MGMT methylated (ref)	ref		ref	
MGMT unmethylated	1.58 (1.27-1.97)	<.001*	1.48 (1.23-.178)	<.001*
MGMT invalid/unknown	1.59 (1.21-2.08)	.001*	1.32 (1.06-1.63)	.012*
HRQoL variables				
Emotional functioning[c]	1.00 (1.00-1.01)	.024*	NS	NS
Fatigue[c]	1.01 (1.00-1.01)	.002*	NS	NS
Nausea and vomiting[c]	1.01 (1.00-1.01)	.011*	1.01 (1.00-1.01)	.008*

OS, overall survival; PFS, progression free survival; HR, Hazard ratio; CI, confidence interval; WHO PS, World Health Organisation Performance Status; Trt, allocated treatment; RT, radiotherapy; chemo, chemotherapy; angio, angiogenesis inhibitor; TTF, tumor-treating fields; HRQoL, health-related quality of life; Ref, reference group in analysis; [a] significant HRQoL variables are presented; [c] continues variable; * statistically significant; NS, non-significant; Models are stratified for disease stage (newly diagnosed/recurrent).

[a] HRs reflect the probability for the event: death in case of OS and progression in case of PFS. HRs of >1 suggest and increased risk of death/progression compared to the reference category, HRs <1 suggest a smaller risk.

References Supplementary file

1. van den Bent, M.J., et al., *Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial.* J Clin Oncol, 2006. **24**(18): p. 2715-22.
2. Stupp, R., et al., *Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma.* New England Journal of Medicine, 2005. **352**(10): p. 987-996.
3. Stupp, R., et al., *Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial.* The lancet oncology, 2014. **15**(10): p. 1100-1108.
4. Baumert, B.G., et al., *Temozolomide chemotherapy versus radiotherapy in molecularly characterized (1p loss) low-grade glioma: A randomized phase III intergroup study by the EORTC/NCIC-CTG/TROG/MRC-CTU (EORTC 22033-26033)*. 2013, American Society of Clinical Oncology.
5. Wick W, Gorlia T, Bendszus M, et al. Lomustine and Bevacizumab in Progressive Glioblastoma. *The New England journal of medicine.* 2017; 377(20):1954-1963.
6. van den Bent MJ, Klein M, Smits M, et al. Bevacizumab and temozolomide in patients with first recurrence of WHO grade II and III glioma, without 1p/19q co-deletion (TAVAREC): a randomised controlled phase 2 EORTC trial. *The Lancet. Oncology.* 2018; 19(9):1170-1179.
7. van den Bent, M.J., et al., Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: a phase 3, randomised, open-label intergroup study. Lancet, 2017. **390**(10103): p. 1645-1653.

8. Wick, W., et al., Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. The lancet oncology, 2012. **13**(7): p. 707-715.
9. Malmström, A., et al., Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. The lancet oncology, 2012. **13**(9): p. 916-926.
10. Keime-Guibert, F., Chinot, O., Taillandier, L., Cartalat-Carel, S., Frenay, M., Kantor, G., Guillamo, J.S., Jadaud, E., Colin, P., Bondiau, P.Y., Menei, P., Loiseau, H., Bernier, V., Honnorat, J., Barrie, M., Mokhtari, K., Mazeron, J.J., Bissery, A., Delattre, J.Y., *Radiotherapy for glioblastoma in the elderly.* N Engl J Med, 2007. **356**(15): p. 1527-1535.
11. Taal W, Oosterkamp HM, Walenkamp AM, et al. Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial. *The Lancet. Oncology.* 2014; 15(9):943-953
12. Chinot, O.L., Wick, W., Mason, W., Henriksson, R., Saran, F., Nishikawa, R., Carpentier, A.F., Hoang-Xuan, K., Kavan, P., Cernea, D., Brandes, A.A., Hilton, M., Abrey, L., Cloughesy, T., *Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma.* N Engl J Med, 2014. **370**(8): p. 709-722.
13. Herrlinger, U., Schafer, N., Steinbach, J.P., Weyerbrock, A., Hau, P., Goldbrunner, R., Friedrich, F., Rohde, V., Ringel, F., Schlegel, U., Sabel, M., Ronellenfitsch, M.W., Uhl, M., Maciaczyk, J., Grau, S., Schnell, O., Hanel, M., Krex, D., Vajkoczy, P., Gerlach, R., Kortmann, R.D., Mehdorn, M., Tuttenberg, J., Mayer-Steinacker, R., Fietkau, R., Brehmer, S., Mack, F., Stuplich, M., Kebir, S., Kohnen, R., Dunkl, E., Leutgeb, B., Proescholdt, M., Pietsch, T., Urbach, H., Belka, C., Stummer, W., Glas, M., *Bevacizumab Plus Irinotecan Versus Temozolomide in Newly*

Diagnosed O6-Methylguanine-DNA Methyltransferase Nonmethylated Glioblastoma: The Randomized GLARIUS Trial. J Clin Oncol, 2016. **34**(14): p. 1611-1619.

14. Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. *European journal of cancer (Oxford, England : 1990).* 2012; 48(14):2192-2202
15. Stupp, R., Taillibert, S., Kanner, A., Read, W., Steinberg, D.M., Lhermitte, B., Toms, S., Idbaih, A., Ahluwalia, M.S., Fink, K., Di Meco, F., Lieberman, F., Zhu, J.J., Stragliotto, G., Tran, D.D., Brem, S., Hottinger, A.F., Kirson, E.D., Lavy-Shahaf, G., Weinberg, U., Kim, C.Y., Paek, S.H., Nicholas, G., Burna, J., Hirte, H., Weller, M., Palti, Y., Hegi, M., Ram, Z., *Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma A Randomized Clinical Trial.* Jama-Journal of the American Medical Association, 2017. **318**(23): p. 2306-2316.